CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Disulfoton (o,o-diethyl s-[2-eththioethyl] phosphorodithioate, Chemical Abstracts Service [CAS] Number 298-04-4, Di-syston) is a systemic organophosphate insecticide/acaricide. It is a manufactured substance and does not occur naturally. Disulfoton was cancelled by the U.S. Environmental Protection Agency (EPA) in 2009 for use as a pesticide, as a result of its toxicity (EPA 2010). Remaining stocks were permitted to be sold until 2011, and its use in U.S. agriculture has been reported as recently as 2016 (USGS 2021). Previously, disulfoton had been used to protect many field and vegetable crops from a variety of harmful insects. As a result of its cancelled use and rapid degradation in air, water, and soil, the potential for human exposure is low. Inhalation and dermal exposures to disulfoton are low for the general population, and exposure in drinking water is likely negligible. Levels of disulfoton in environmental media are also expected to be low. People who previously manufactured, handled, or applied disulfoton or who were involved in the disposal of disulfoton were at a higher risk of exposure than the general population. Occupational exposure is expected to be negligible in the United States since its cancellation. People who live near disulfoton manufacturing or processing sites, or hazardous waste sites containing disulfoton may be at higher risk of exposure.

Toxicokinetic data show that disulfoton is readily and extensively absorbed by the gastrointestinal tract. The urinary metabolites of disulfoton are diethyl phosphate (DEP), diethyl thiophosphate (DETP), diethyl dithiophosphate (DEDPT), and diethyl phosphorothiolate (DEPTh). Although the occurrence of these phosphate esters in human urine may not result specifically from exposure to disulfoton, detection of these metabolites in human urine indicates the possibility of exposure to disulfoton or several other organophosphate insecticides.

1.2 SUMMARY OF HEALTH EFFECTS

Information on disulfoton toxicity comes primarily from oral studies on laboratory animals, followed by inhalation studies on laboratory animals and a few human case studies of oral ingestion of disulfoton. Toxicity studies on disulfoton have evaluated a variety of endpoints, primarily neurological, respiratory, endocrine, reproductive, and developmental. The genotoxicity of disulfoton has also been tested on a variety of species test systems.

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As displayed in Figures 1-1 and 1-2, the most sensitive endpoints for disulfoton toxicity appear to be neurological and developmental. A systematic review was conducted on these endpoints. Weight-of-evidence conclusions are defined in Appendix C. The review resulted in the following hazard identification conclusions.

- Developmental effects are a presumed health effect following oral exposure.
- Neurological effects are a presumed health effect following oral exposure.
- Neurological effects are a presumed health effect following inhalation exposure.
- Neurological effects are not classifiable (defined as a low level of evidence in human studies and a low level of evidence in animal studies) following dermal exposure.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Disulfoton

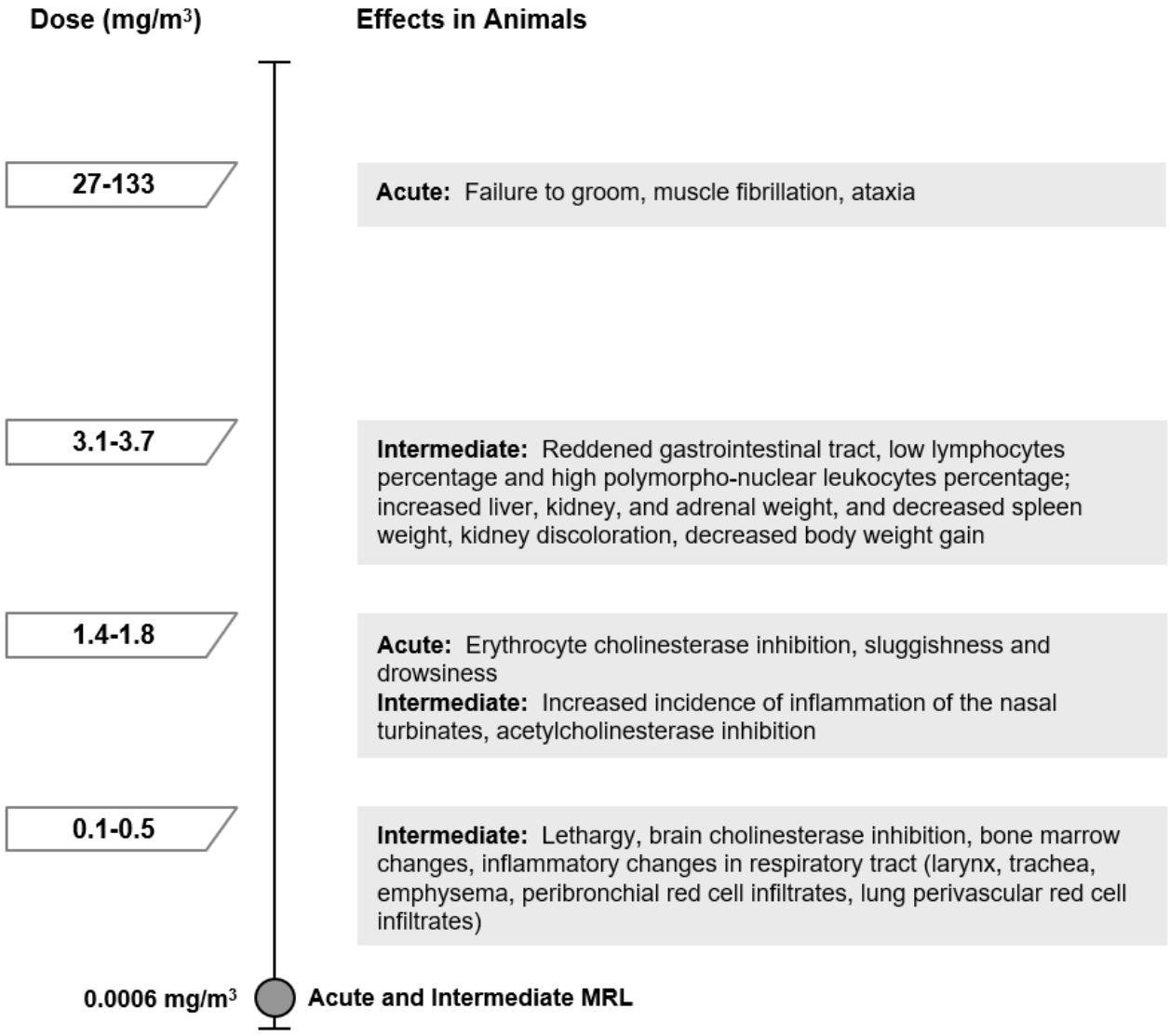
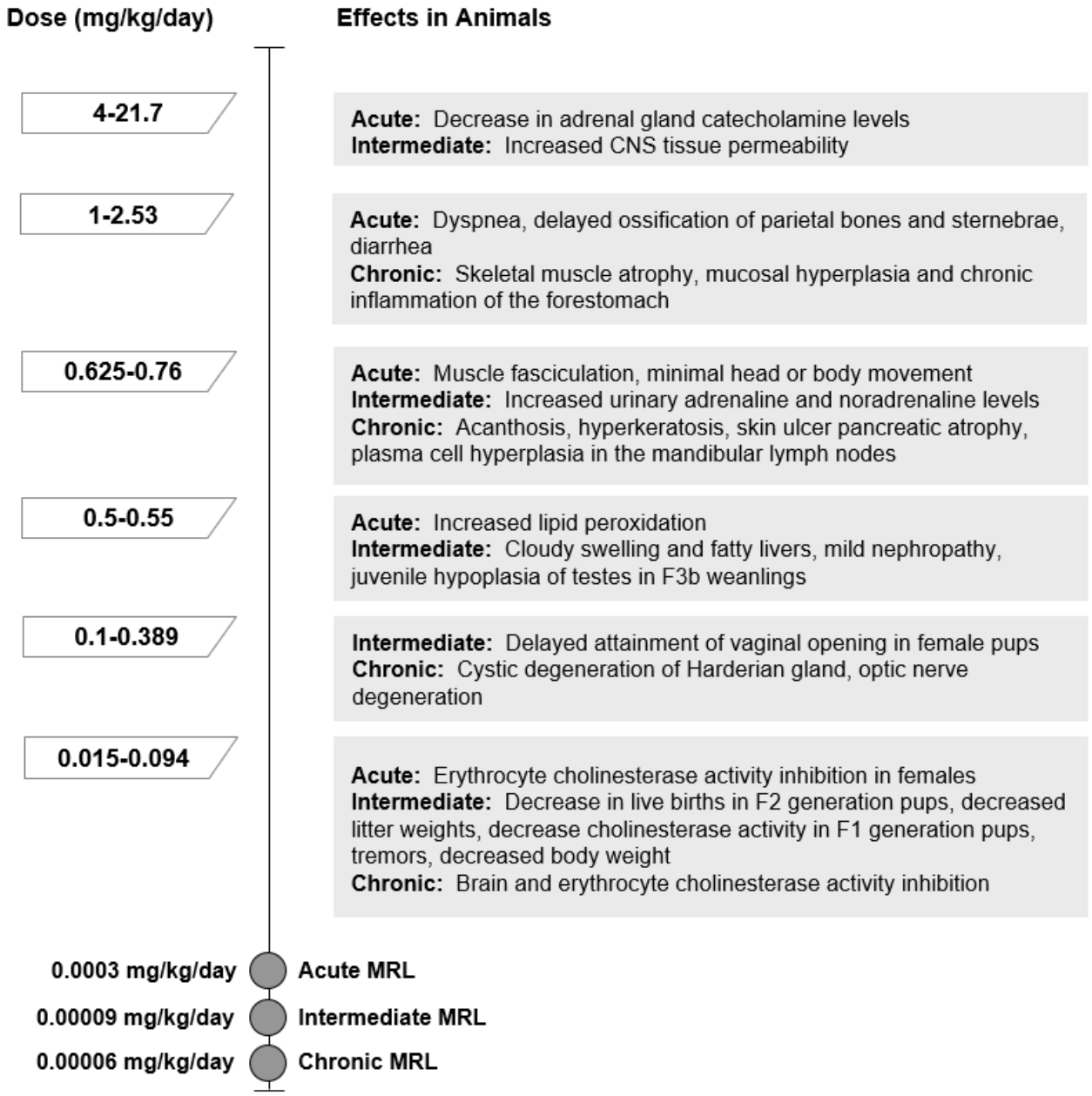


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Disulfoton



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Developmental Effects. Studies in laboratory animals support developmental toxicity as a sensitive endpoint following oral exposure to disulfoton. Following oral exposure of both parents, or maternal only, to disulfoton, rat offspring showed significant inhibition of brain or red blood cell acetylcholinesterase (AChE) activity (Hixson and Hathaway 1986; Klaus 2006c; Ryan et al. 1970; Sheets 2005; Taylor 1965a). No cholinergic signs of toxicity were noted at the doses tested in these studies, and no treatment-related effects were seen in a functional observational assessment performed in one study (Sheets 2005). Female pups exposed *in utero* and during lactation had delayed vaginal opening, a developmental milestone (Sheets 2005). Additionally, in a multi-generational exposure study, third-generation offspring had significantly depressed red blood cell AChE activities (Taylor 1965a). Swelling of the liver, mild nephropathy, and juvenile hypoplasia of the testes were also observed, likely resulting from exposure during gestation (Taylor 1965a). These findings are consistent with significant cholinesterase inhibition and related cholinergic toxicity observed in animals and humans following oral exposure to disulfoton.

Neurological Effects. Numerous inhalation and oral studies in laboratory animals and a few human studies strongly support nervous system effects as the most sensitive endpoint following exposure to disulfoton. Cholinesterase inhibition results in the accumulation of acetylcholine at synapses and neuromuscular junctions. This accumulation overstimulates the cholinergic systems, which can result in various adverse neurological outcomes such as headache, vertigo, and confusion. Human occupational studies have shown significant depression of AChE activity following oral and dermal exposure (Wolfe et al. 1978) and neurological symptoms including headaches, nausea, weakness, and fatigue (Gómez-Arroyo et al. 2000). These findings are further corroborated by findings in numerous human case studies where clinical findings have measured severely depressed cholinesterase activity and muscarinic effects alongside signs of intoxication including confusion, vomiting, masseter muscle spasms, and other symptoms (Futagami et al. 1995; Hattori et al. 1982; Savage et al. 1971; Yashiki et al. 1990). These studies are limited as levels of exposure associated with these effects could not be measured. Additionally, lifestyle factors, such as smoking, for individuals were not sufficiently assessed; this limitation increases the risk of bias (Futagami et al. 1995; Gómez-Arroyo et al. 2000; Hattori et al. 1982; Wolfe et al. 1978; Yashiki et al. 1990). In animal studies, excessive accumulation of acetylcholine and catecholamines has been observed after dosing with disulfoton. Significant AChE inhibition is the primary neurological effect observed in rats across a wide range of oral doses and inhalation concentrations (Costa and Murphy 1983a; Costa et al. 1986; EPA 2007; Hayes 1983, 1985; Klaus 2006a, 2006b; 2006c; Matsuda et al. 2000; Sheets 1993a, 1993b; Shiotsuka 1989; Schwab and Murphy 1981; Schwab et al. 1983; Stavinoha et al. 1969; Su et al. 1971; Thyssen 1978, 1980; Yagle and Costa 1996).

Among these studies, many have observed inhibition to be dose-dependent. In addition to these studies, typical clinical signs of cholinergic toxicity and depression have been observed in mice and rats, including sluggishness, muscle twitching, ataxia, tremors, dyspnea, and convulsions (Crawford and Anderson 1974; Doull 1957; Flucke 1986; Mihail 1978). Neurotoxic signs have occurred in pregnant laboratory animals, including muscular tremors and severe inhibition of cholinesterase activity (Hixson and Hathaway 1986; Klaus 2006c; Lamb and Hixson 1983; Tesh et al. 1982). Additionally, female animals across multiple studies have been found to be more susceptible than male rats to cholinergic effects of disulfoton (Carpy et al. 1975; Jones et al. 1999; Klaus 2006b; Rivett et al. 1972; Thyssen 1978); however, the cause of this observation was not further examined. Studies are inconclusive on the whether disulfoton alters behavior or functional task performance in animals (Clark and Pearson 1973; Clark et al. 1971; Flucke 1986; Jones et al. 1999; Sheets 1993a).

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, following inhalation exposure, the neurologic system is the most sensitive target with the highest level of evidence associated with disulfoton exposure. The inhalation database was considered adequate for derivation of an intermediate-duration MRL for disulfoton. Additionally, the intermediate-duration MRL was adopted as the as the acute-duration inhalation MRL as it is considered protective of acute-duration inhalation exposure to disulfoton. However, a chronic-duration inhalation MRL was not developed as the database was inadequate. For oral exposure (Figure 1-4), the available data suggest that neurological, reproductive, developmental, and ocular endpoints are sensitive targets in animals. The oral database was considered adequate for the derivation of acute-, intermediate-, and chronic-duration oral MRLs for disulfoton. MRLs derived for the inhalation and oral-exposure routes for disulfoton are summarized in Table 1-1, and are discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Disulfoton – Inhalation

The neurological endpoint is the most sensitive target of disulfoton inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

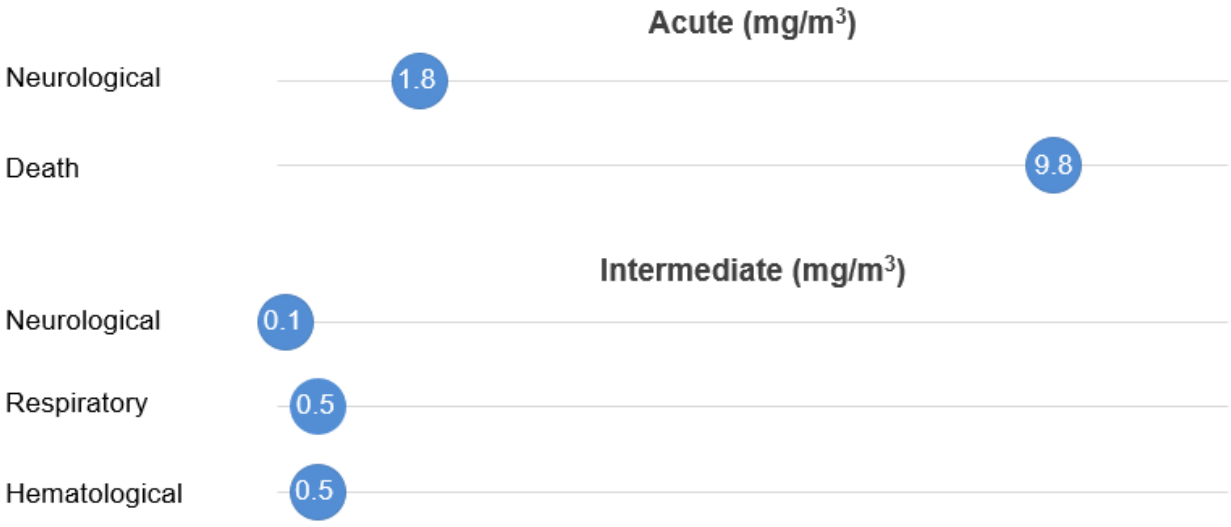

Figure 1-4. Summary of Sensitive Targets of Disulfoton – Oral

The neurological and developmental endpoints are the most sensitive targets of disulfoton oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

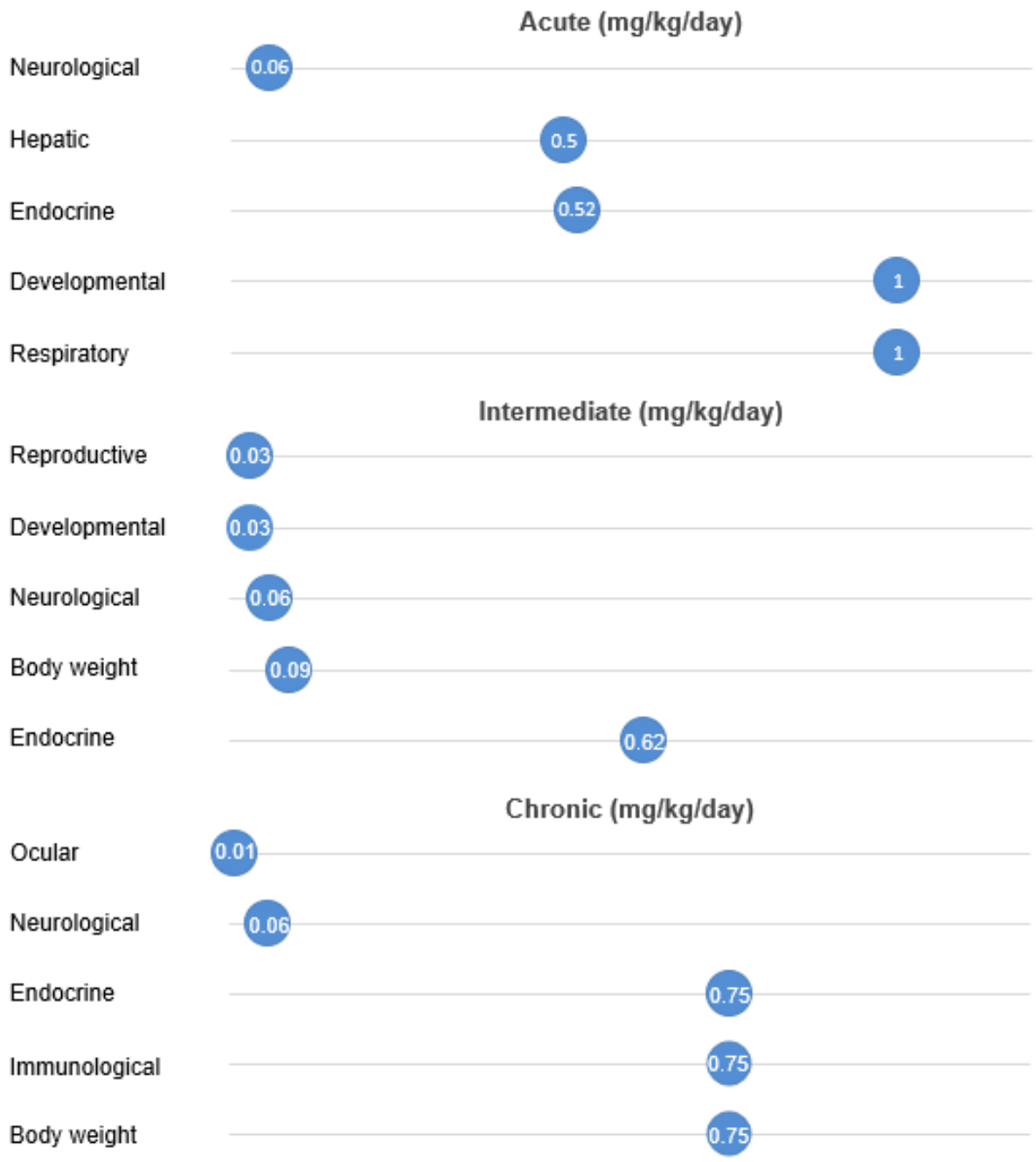

Table 1-1. Minimal Risk Levels (MRLs) for Disulfoton[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (mg/m^3)					
Acute	The intermediate-duration inhalation MRL of **0.0006 mg/m^3 (0.6 µg/m^3)** is adopted as the acute-duration inhalation MRL				
Intermediate	**0.0006 (0.6 µg/m^3)**	Decreased brain AChE activity	NOAEL: 0.1 ($NOAEL_{HEC}$: 0.018)	30	Thyssen 1980
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg/kg/day)					
Acute	**0.0003 (0.3 µg/kg/day)**	Decreased red blood cell AChE activity	$BMDL_{20RD}$: 0.028	100	Klaus 2006b
Intermediate	**0.00009 (0.09 µg/kg/day)**	Decreased brain AChE activity	NOAEL: 0.009	100	Hixson and Hathaway 1986
Chronic	**0.00006 (0.06 µg/kg/day)**	Decreased red blood cell AChE activity	LOAEL: 0.06	1,000	Hayes 1985

[a]See Appendix A for additional information.

AChE = acetylcholinesterase; $BMDL_{20RD}$ = benchmark dose lower bound with 20% relative deviation; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level